



Pachyonychia Congenita Project

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We hope that making available the relevant information on Pachyonychia Congenita will be a means of furthering research to find effective therapies and a cure for PC.

A severe case of pachyonychia congenita type I due to a novel proline mutation in keratin 6a

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Pachyonychia congenita (PC) is an autosomal dominantly inherited ectodermal dysplasia with variable expression and high penetrance.¹ The major features of the syndrome are hypertrophic nail dystrophy, palmoplantar keratoderma and oral leucokeratosis, accompanied by other ectodermal defects, according to subtype.² Defects in keratins expressed within the nail bed have been found to underlie the two major variants of PC.^{3,4} Specifically, keratin K6a or K16 mutations cause type I/Jadassohn–Lewandowsky syndrome (PC-1), and K6b or K17 abnormalities result in type II/Jackson–Lawler syndrome (PC-2). We report a new mutation in the K6a gene in a sporadic case of PC-1 with a severe clinical presentation.

Case and methods

A 30-year-old woman presented with thick nails, hyperkeratotic skin lesions on both feet and oral leucoplakia. Whitish plaques on the buccal mucosa had been present since the first months of life, and at this time the toenails became thickened with a yellow greyish colour. Similar fingernail changes soon followed. When she started walking, she suffered recurrent blistering and crust formation on the soles of her feet, followed by gradual development of thick plantar keratoderma. Now, in adulthood, painful fissuring of the soles makes walking very difficult, especially during summer. There was neither consanguinity in the family nor a history of similar cutaneous findings. Physical examination revealed typical symmetrical thickening of all fingernails and toenails (Fig. 1a,b). Yellowish thick plaques with fissures on both soles were also observed and there was extensive oral leucokeratosis (Fig. 1c,d). She had also follicular hyperkeratosis on the buttocks, elbows and knees (not shown). There were no hair anomalies, hoarseness, natal teeth or the pilosebaceous cysts diagnostic of PC-2. Biopsy of a typical plantar lesion showed

psoriasiform hyperplasia and parakeratosis. The basal layer contained keratinocytes with wide, clear cytoplasm. In the dermis there was a perivascular infiltrate composed mainly of lymphocytes (Fig. 1e).

Several topical treatments including lubricants, emollients, keratolytics such as salicylic acid, antibiotics, antiseptic wet dressings, hydrocolloid dressings, chromium mercury solution, corticosteroid cream, retinoid cream and coal tar had been tried in the past, with no success. The patient had also been treated with etretinate 25 mg daily, vitamin A 50 000–100 000 U daily and erythromycin 500 mg three times daily, with only slight improvement. Oral corticosteroids, up to 30 mg daily, and nonsteroidal anti-inflammatory drugs produced only transient benefit. Only ibuprofen 1200 mg daily gave some subjective improvement. Mycological cultures from nails and whitish plaques on the tongue were normal.

Results and discussion

Molecular genetic analysis, as described previously,⁵ identified a novel defect in K6a. Direct sequencing of genomic polymerase chain reaction products revealed a heterozygous missense mutation 1390A → C in exon 7 of the KRT6A gene (Fig. 2). This mutation predicts the amino acid change threonine to proline (T464P) in the helix termination motif of the K6a polypeptide. The mutation was excluded from 60 normal unrelated controls by restriction enzyme analysis (NlaIV site created with mismatch primer; data not shown). This particular defect has not been reported previously, although there have been two nearby mutations (L469R and E472K) in the helix 2B domain of the K6a protein, which is a recognized keratin mutation 'hot-spot' (Intermediate Filament Mutation Database: <http://www.interfil.org>). The amino acid proline is particularly disruptive to α -helical tertiary structures



Fig 1. (a) Hypertrophic dystrophy of the toenails and keratoderma of the plantar surfaces. (b) Dystrophy of the fingernails. (c) Plantar keratoderma with severe fissures. (d) Oral cavity with irregularly shaped whitish plaques (oral leukokeratosis). (e) Biopsy specimen of plantar skin shows psoriasiform hyperplasia, parakeratosis and areas of suprabasal keratinocytes with wide, clear cytoplasm.

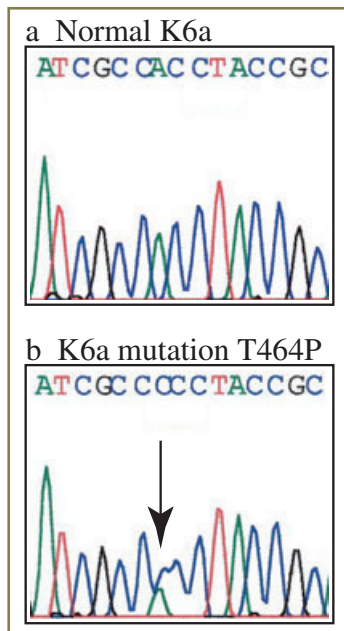


Fig 2. (a) Normal K6a exon 7 sequence (+ strand) corresponding to codons 462–466. (b) Same region as shown in (a) from the affected individual showing heterozygous missense mutation 1390A → C (arrow) predicting amino acid change T464P.

in proteins, and proline mutations have been reported in other moderate-to-severe cases of PC.⁶ This might help explain the more severe symptoms in the patient, although there are

undoubtedly other modifying factors at play in PC and other keratin disorders.⁷

Our patient presented with all the features of PC-1 (nail changes, palmoplantar hyperkeratosis, follicular keratosis and oral leukokeratosis). Although PC might appear to be primarily a cosmetic disorder, the physical disability resulting from the severe and very painful keratoderma can have a substantial impact on quality of life, as is illustrated by our patient (Fig. 1). At the present time, there is no curative treatment for PC and therefore therapeutic efforts should be directed towards improving symptoms that cause significant disability. Numerous treatments have been tried in PC, with little success.⁸ Surgical removal of the abnormal nails may not be helpful because the dystrophic nail can regrow and, similarly, systemic retinoid therapy produces inconsistent results.^{9,10} Very recently, an international PC charity has been established offering advice for patients and their clinicians, genetic testing and funding research into novel treatments (<http://www.pc-project.org>). These new initiatives will help support patients with PC presently and will hopefully lead to the development of more efficacious therapies for this debilitating genodermatosis in the future.

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